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TITLE: Targeting homology-directed recombinational repair (HDR) of chromosomal breaks to sensitize prostate cancer cells to poly (ADP-ribose) polymerase (PARP) inhibition

PRINCIPAL INVESTIGATOR: Shih-Hsin Eddy Yang, M.D., Ph.D.

CONTRACTING ORGANIZATION: University of Alabama at Birmingham
Birmingham, AL 35294 – 0111

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14. ABSTRACT

Previous reports suggest radiation induces BRCA1 nuclear export. We thus hypothesized that in prostate cancer cells, radiation will induce BRCA1 nuclear export and subsequently render tumor cells homologous recombination repair deficient. This, then, would render tumor cells susceptible to PARP inhibition, which target cells that are deficient in homologous recombination repair.

15. SUBJECT TERMS
BRCA1 export, synthetic lethality, PARP inhibition

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Final Report August 2013

Title: *Targeting homology-directed recombinational repair of chromosomal breaks to sensitize prostate cancer cells to poly (ADP-ribose) polymerase (PARP) inhibition*

Principal Investigator: Shih-Hsin Eddy Yang, M.D., Ph.D.

INTRODUCTION: Agents that target cancers which are deficient in double strand break (DSB) repair, such as poly (ADP-ribose) polymerase-1 (PARP1) inhibitors, have been demonstrated to have highly selective killing (57 fold) of BRCA1-mutated tumors while maintaining minimal toxicity in normal tissues[1-5]. However, the majority of prostate cancers carry wild-type(WT) BRCA1[6,7] and express elevated BRCA1 levels compared to normal prostate tissue[8]. Thus, to enhance the utility of PARP1 inhibitors in patients with prostate cancer, we proposed to sequester WT-BRCA1 from the nucleus where DSBs are repaired to the cytoplasm where apoptosis is activated to render a DSB repair defect and augment the cytotoxic response to PARP1 inhibition in prostate tumor cells. By inducing a DSB repair deficiency, sensitization of prostate cancers to PARP1 inhibitors can be an innovative therapeutic strategy and enhance therapeutic ratio for the majority of patients with prostate cancer.

BODY: We proposed the following tasks for the duration of the grant period as stated below and report the outcomes as follows:

Task 1. **Determine whether IR-induced BRCA1 nuclear export will sensitize prostate cancer cells to PARP1 inhibition, and to determine whether these effects are dependent on CRM1 (Months 1-12):**

A) Assess the sensitivity of irradiated prostate cancer cells to PARP1 inhibition (Months 1-6)
   a. Dose response to varying doses of IR (2 – 4Gy) and BRCA1 location by IHC
   b. Time course of BRCA1 nuclear export following IR (4-48hrs following IR)
   c. Sensitivity of irradiated prostate cancer cells to PARP1 inhibition (dose and time factors) via soft agar colony formation ability

B) Determine whether sensitization of irradiated prostate cancer cells to PARP1 inhibition is dependent on CRM1 (Months 6-12)
   a. Dose response of leptomycin B to inhibit IR-induced BRCA1 nuclear export
   b. Sensitivity of irradiated prostate cancer cells to PARP1 inhibition following blockade of IR-induced, CRM1-mediated BRCA1 nuclear export

RESULTS:

Task 1A. We have performed time course and dose response of LNCaP cells to 2-4 Gy IR and assessed BRCA1 location following such treatment. Interestingly, as shown in Fig.1, BRCA1 subcellular localization is altered (reduced nuclear with concomitant increased cytosolic) as early as16 hrs following IR and persists up to 72hrs (data not shown). Doses of IR as low as 3Gy can achieve this shift of BRCA1 from the nucleus to the cytoplasm.

Given that IR can shift BRCA1 from the nucleus to the cytoplasm away from its repair substrates, we next hypothesized that prostate cancer cells exposed to IR will subsequently have a homology-directed recombination repair defect. To test this hypothesis, we utilized LNCaP cells stably expressing the DRGFP HDR repair substrate. In this assay, HDR activity correlates with GFP expression following the induction of a DSB generated by a restriction endonuclease. As shown in Fig. 2, IR indeed reduced % of GFP positive cells.

Lastly, given that IR reduces nuclear BRCA1 and subsequently generates a HDR repair defect, we next assessed tumor susceptibility to PARP inhibition following IR. Consistent with our hypothesis, sensitivity of irradiated prostate cancer cells to the PARP inhibitor ABT-888 as assessed by colony formation assays is augmented (Fig. 3).

These results suggest that IR generates a HDR repair defect by sequestering BRCA1 in the cytoplasm and subsequently, prostate tumor cells are rendered susceptible to PARP inhibition.

Additionally, it was previously reported that IR-induced BRCA1 nuclear export in breast cancer cells is dependent on p53. To assess whether BRCA1 nuclear export following IR in prostate cancer cells is also p53 dependent, we next performed the above experiments in PC-3 prostate cancer cells, which are deficient in p53. As shown in Fig. 4, IR does not result in BRCA1 nuclear export in PC-3 cells. Given this finding, we hypothesized that IR would not augment PC-3 cellular susceptibility to PARP inhibition. This is indeed what is observed (Fig. 5).

Task 1B. Previous reports suggest that IR-induced BRCA1 export is also dependent on CRM1. To test this hypothesis, we proposed that the CRM1 inhibitor leptomycin B would inhibit IR-induced BRCA1 export. As shown in Fig. 6, in the presence of leptomycin B, BRCA1 export is no longer apparent following IR. Additionally, leptomycin B prevented the IR-induced deficiency in HR (Figure 7), and subsequently prevent IR-induced synthetic lethality with PARP inhibition in LNCaP prostate cancer cells (Figure 8). Taken together, our data suggest that indeed IR induces BRCA1 nuclear export to generate a HR deficiency, which subsequently sensitizes prostate tumor cells to PARP inhibition. These effects are all dependent on CRM1, as leptomycin B, which inhibits CRM1, abrogates the observed effects.

KEY RESEARCH ACCOMPLISHMENTS FOR TASK 1:

- IR induces BRCA1 nuclear export in LNCaP but not the p53 deficient PC-3 cells
- IR generates a HDR repair defect in LNCaP cells
- IR induces synthetic lethality with PARP inhibition in LNCaP cells but not PC-3 cells
- Inhibition of CRM1 with leptomycin B abrogates IR-mediated BRCA1 export
- Inhibition of CRM1 with leptomycin B abrogates the IR-induced HR deficiency
- Inhibition of CRM1 with leptomycin B abrogates synthetic lethality of IR and PARP inhibition

FIGURES FOR TASK 1:

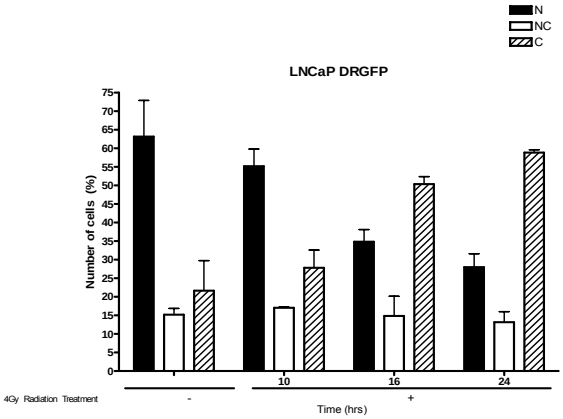

Figure1. IR increases cytosolic BRCA1 and reduces nuclear BRCA1 in LNCaP human prostate cancer cells.

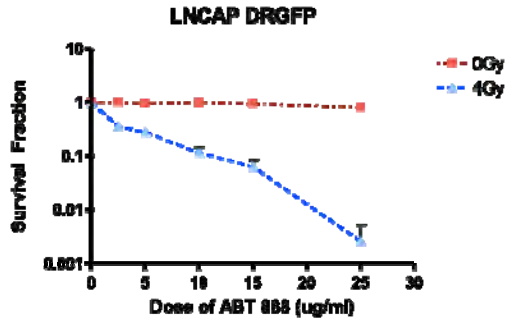

Figure 3. IR induces synthetic lethality with the PARP inhibitor ABT-888.

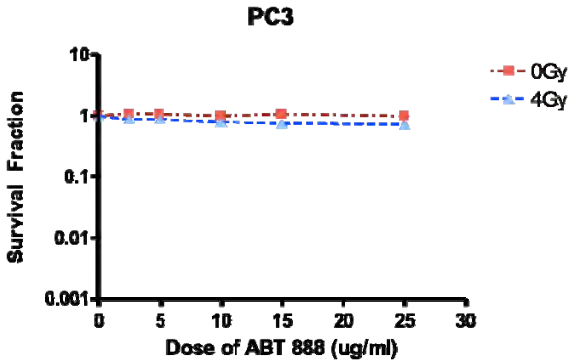

Figure 5. IR does not induce synthetic lethality with ABT-888 in PC-3 human prostate cancer cells.

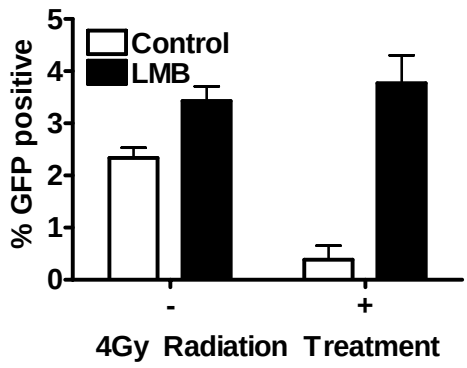

Figure 7. Leptomycin B abolishes the HR deficit induced by HR. additionally, it may enhance HR.

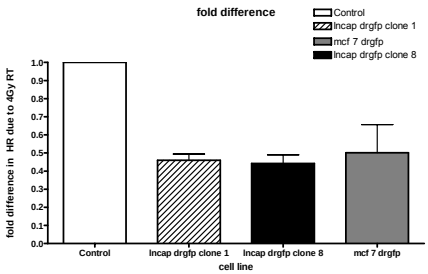

Figure 2. IR reduces HR repair in LNCaP human prostate cancer cells.

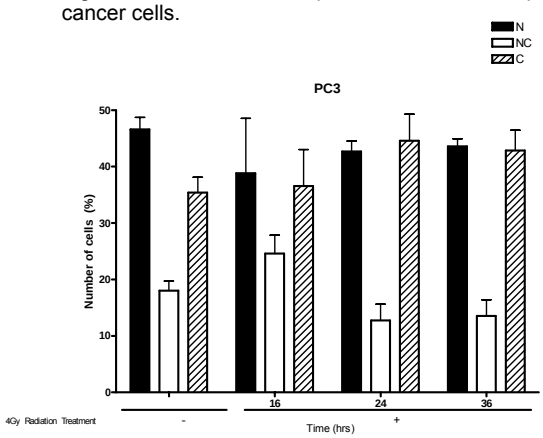

Figure 4. IR does not alter BRCA1 subcellular location in the p53 null PC-3 human prostate cancer cell line.

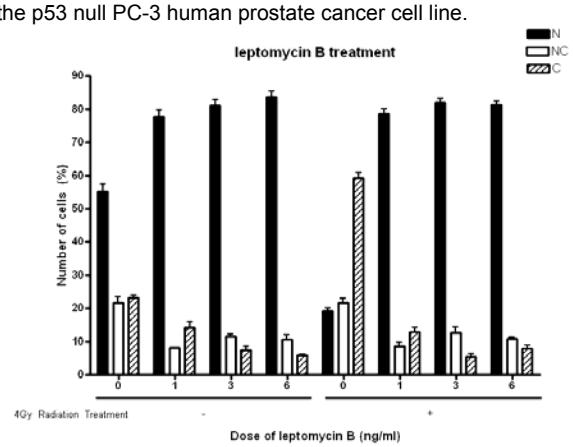

Figure 6. IR induced BRCA1 nuclear export is inhibited by leptomycin B, suggesting CRM1 dependence.

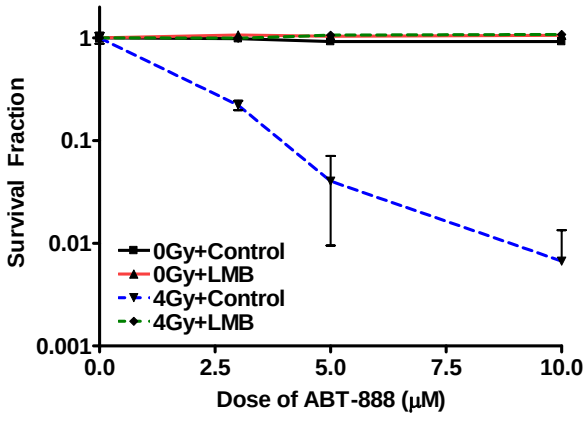

Figure 8. Leptomycin B abolishes synthetic lethality between IR and PARP inhibition.

Task 2. **To transiently reduce nuclear BRCA1 using a tetracycline (tet)-regulated expression of tr-BRCA1 and determine its effects on HDR and sensitivity to PARP1 inhibition in prostate cancer cells (Months 12-24).**

A) Generate the LNCaP$^{tr\text{-}BRCA1\text{-}TETOFF/DRGFP}$ stable cell line and validate tet-repressible expression of tr-BRCA1 via Western blot and integrated HDR reporter substrate by flow cytometry (Months 12-15)
B) Validate tr-BRCA1-mediated BRCA1 nuclear export in clones via IHC (Months 16-18)
C) Determine HDR capacity in LNCaP$^{tr\text{-}BRCA1\text{-}TETOFF/DRGFP}$ cells with and without tr-BRCA1 using flow cytometric assessment of GFP expression (Months 18-21)
D) Determine sensitivity of LNCaP$^{tr\text{-}BRCA1\text{-}TETOFF/DRGFP}$ cells to PARP inhibition with and without tr-BRCA1 using soft agar colony formation ability (Months 21-24)

RESULTS:

We have continued to be unsuccessful in generating stable cell lines expressing both the DRGFP repair substrate as well as the inducible tr-BRCA1. However, as we reported in the progress report 2012, we were able to perform most of our proposed experiments using a transiently transfected inducible tr-BRCA1 when needed. As shown in figure 9, tr-BRCA1 indeed induces BRCA1 nuclear export in both LNCaP (p53 wt) and PC-3 (p53 null) cells. In LNCaP cells, tr-BRCA1 effects are compared with IR (left panel). For PC-3 cells, a time course was performed (right).

Additionally, HR capacity was indeed reduced by tr-BRCA1 (Figure 10). Lastly, consistent with our hypothesis, tr-BRCA1 reduced colony forming ability of LNCaP and PC-3 cells when combined with the PARP inhibitor ABT-888 (Figure 11).

Furthermore, we attempted to assess the mechanism of cytotoxicity observed in prostate cancer cells treated with radiation followed by PARP1 inhibition. Because of our previous findings in other cancer types such as head and neck and triple negative breast cancer (Nowsheen, S, et al. PLOS One 2011; Nowsheen et al. PLOS One 2012), we first hypothesized that the mechanism is due to activation of apoptosis. Interestingly, we could not detect cleavage of caspase-3 as our marker for apoptosis. We also attempted Annexin V analysis by flow cytometry and did not observe any differences amongst our treatment groups (data not shown). Other reports suggest cytotoxicity of PARPi, in particular in prostate cancer, is due to changes in cell cycle distribution, especially accumulation in the G2/M phase. Thus, we assessed cell cycle distribution using flow cytometry following our various treatments.

As shown in Figure 12, indeed in the LNCaP prostate cancer cells, which are sensitive to the therapeutic strategy of radiation followed by PARPi, there is an increase in the proportion of cells in the G2/M cell cycle phase. In contrast, the cell cycle distribution of PC-3 cells, which are insensitive to these treatments, is not changed. Furthermore, we assessed whether persistent DNA damage as measured by persistent g-H2AX foci is observed in cells sensitive to the combination. Indeed this is the case (Figure 13). We are currently continuing to investigate whether these mechanisms are also observed using Tr-BRCA1.

KEY RESEARCH ACCOMPLISHMENTS FOR TASK 2:

- Tr-BRCA1 induces BRCA1 nuclear export in LNCaP and PC-3 cells
- Tr-BRCA1 generates a HR repair defect in LNCaP cells
- Tr-BRCA1 induces synthetic lethality with PARP inhibition in LNCaP and PC-3 cells
- Cytotoxicity of LNCaP cells with radiation and PARPi is due to increased proportion of cells in G2/M phase of the cell cycle and correlates with persistent DNA damage.

FIGURES FOR TASK 2:

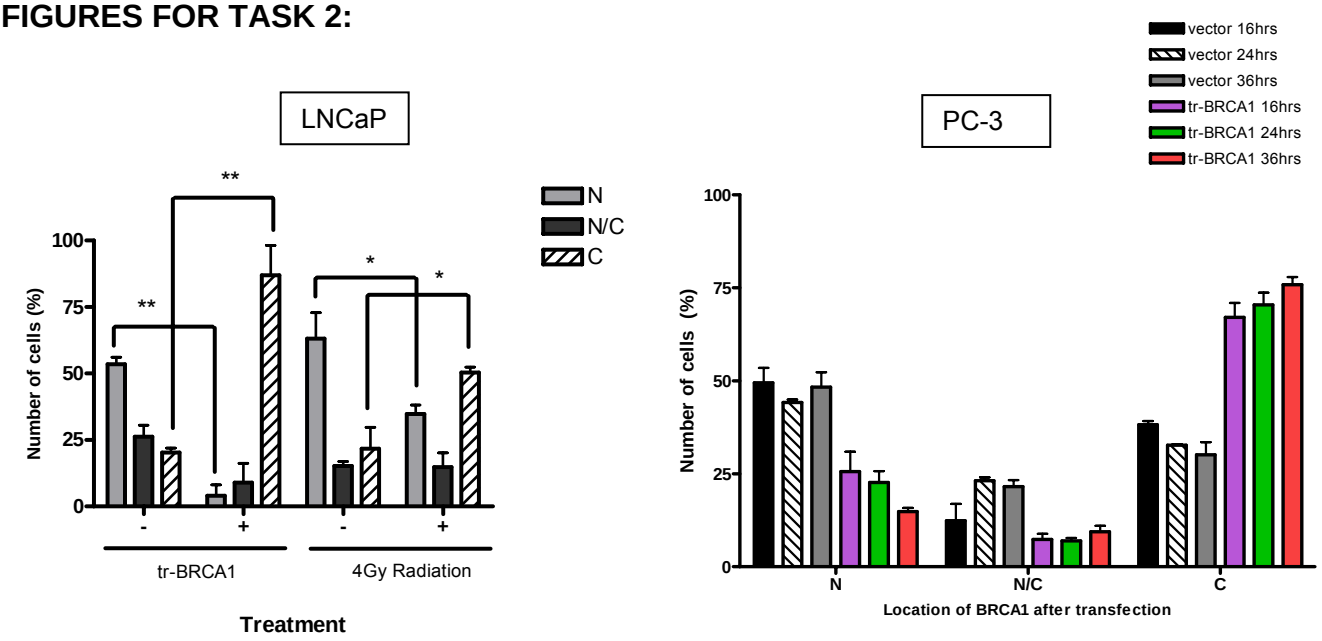

Figure 9. Tr-BRCA1 induces BRCA1 nuclear export independent of p53 status.

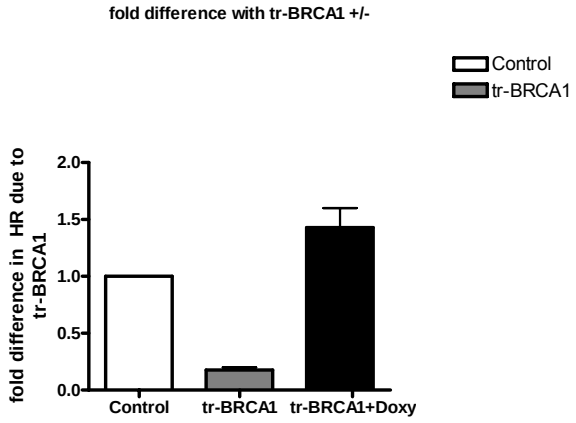

Figure 10. Tr-BRCA1 inhibits HR repair, while doxycycline, which turns off tr-BRCA1 expression, enhances repair.

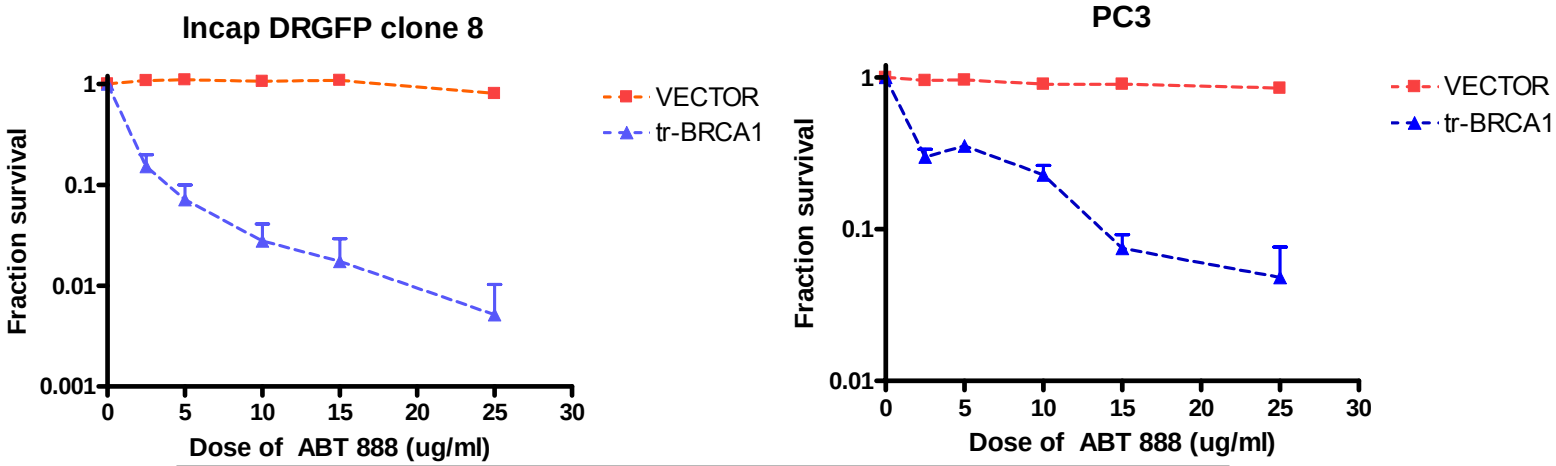

Figure 11. Tr-BRCA1 induces synthetic lethality with PARPi in LNCaP (left) and PC-3 (right).

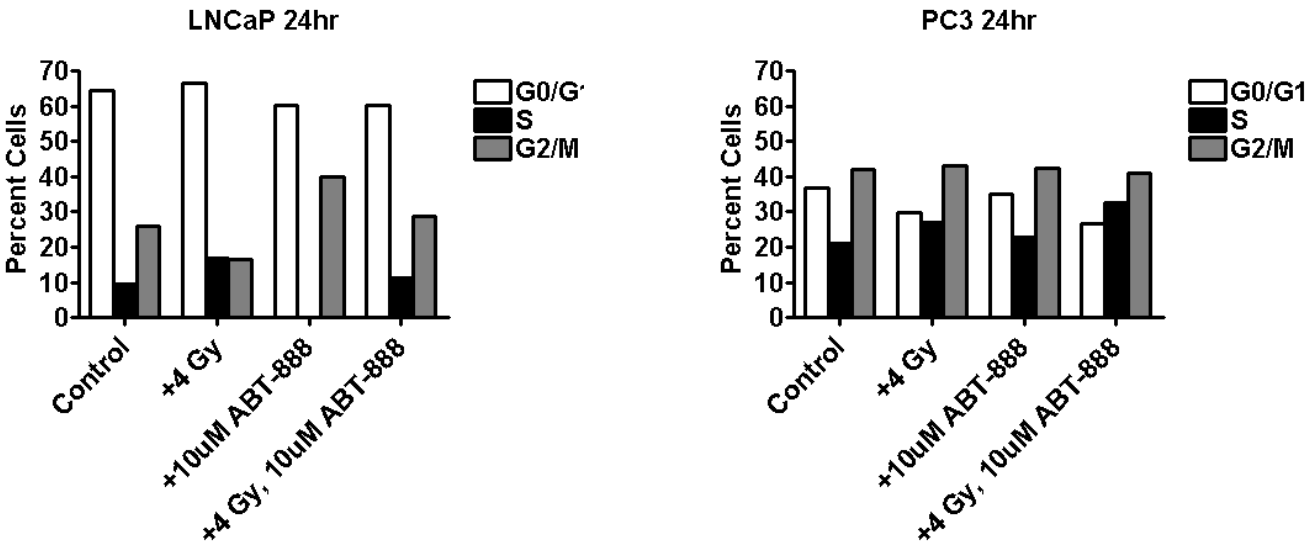

Figure 12. Synthetic lethality with radiation and PARPi in LNCaP (left) cells may be due to accumulation of cells in G2/M phase of the cell cycle induced by PARPi ABT-888. These effects are not observed in the PC-3 cells (right).

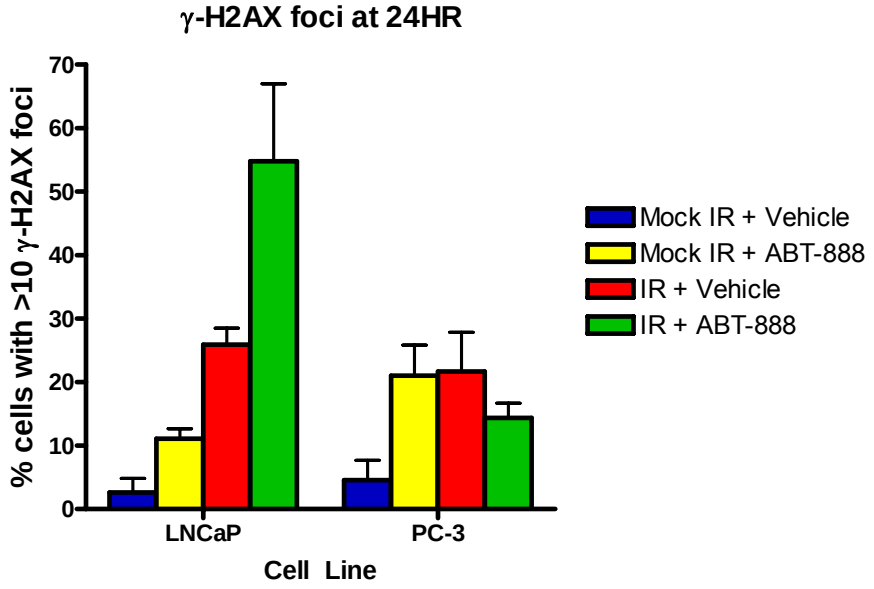

Figure 13. Synthetic lethality with radiation and PARPi in LNCaP (left) cells correlates with persistent DNA damage. These effects are not observed in the PC-3 cells (right).

Task 3. **To validate the role of induced DSB repair deficiency and sensitivity to PARP1 inhibition *in vivo* with prostate tumor xenograft models (Months 24-36).**

A) Determine optimal cell number for grafting of LNCaP xenografts in mice (Months 24-36)
B) To assess sensitivity of irradiated prostate tumor xenografts to PARP1 inhibition by tumor growth delay assays (Months 24-36)
C) To assess resistance of prostate tumor xenografts to PARP1 inhibition following tet-repression of tr-BRCA1 expression by tumor growth delay assays (Months 24-36).

RESULTS*:*

Unfortunately, we were unsuccessful in generating prostate cancer xenografts despite varying the tumor cell number. Our initial experiment was started 12/14/2011. We injected 35 athymic nude mice with 10 million LNCaP cells in each flank. These did not take.

Our second trial was 3 months later 3/21/2012, with inoculation of 2.5 million LnCap cells into both flanks of again 35 male athymic nude mice.We used a 2:1 ratio matrigel:cells in media (per Dr. Buchsbaum's (mentoring committee member with extensive animal model experience) suggestion; these also were not successful in growing LnCap). Treatment groups were going to be:

Left- 0 Gy
1. Control
2. ABT-888
Right- 4 Gy
1. Control
2. ABT-888

Due to the low take rate of the Lncap cell line (<20%) and the slow progression of tumor growth once it was established (4-6 months), we have not been able to accumulate adequate results at this time. Tumors were collected 6 months post-inoculation on 9/27/12 as follows:

One tumor from flank of one mouse was minced into 1-2 mm fragments
-5 vials with 10% DMSO, 10% FBS, 50 U/ml heparin in DMEM
-5 vials with 10% DMSO in DMEM
-stored in -80 C for re-implantation

4 small tumors (3 different mice, one mouse had both L and R flank tumors), and 1 large tumor were collected and fresh frozen, stored at -80 C for protein extraction to be used in Western blotting.

We are currently awaiting IACUC approval for our protocol modification to allow for implanting the "successful" xenografts as explants corrected for tumor weight to perform the proposed experiments.

REPORTABLE OUTCOMES:

We have presented data generated from this training grant at the ASTRO Annual Meeting 2010 and 2011. Both were invited oral presentations. Additionally, the 2010 presentation won the basic science award at ASTRO. We are currently preparing a manuscript to report the results of our study supported by this DOD grant.

Importantly, training that occurred as a result of this grant has stimulated other research projects that investigate other methods of targeting DNA repair to render tumor cells susceptible to PARP inhibition. These projects have resulted in multiple grant awards, including a translational scholar award from the Sidney Kimmel Foundation for Cancer Research, and a career development award from the AACR/Genentech BioOncology. Most recently, we received a career catalyst award from the Susan G. Komen Foundation for Cancer Research. We have also submitted grant applications to the American Cancer Society as well as Department of Defense BCRP and have become a UAB Breast SPORE Project (Project 2) that is currently under review.

Also, publications have resulted as a result of these "spin-off" projects. They are listed as follows:

1. Nowsheen, S, Bonner, JA, **Yang, ES*.** The poly (ADP-Ribose) polymerase inhibitor ABT-888 reduces radiation-induced nuclear EGFR and augments head and neck tumor response to radiotherapy. *Radiother Oncol* 2011. 99: 331 – 338. ***Corresponding author**
2. Nowsheen, S, Trummell, H, Whitley, AC, Dobelbower, MC, LoBuglio, AF, Bonner, JA, **Yang, ES*.** Cetuximab induces synthetic lethality with poly (ADP-Ribose) polymerase inhibition in head and neck cancer. *PLOS One* 2011. 6: e24148. ***Corresponding author.**
3. Nowsheen, S, Cooper, T, Bonner, JA, LoBuglio, AF, **Yang, ES***. HER2 overexpression renders human breast cancers sensitive to PARP inhibition independently of any defect in homologous recombination DNA repair. Cancer Research 2012. 72(18): 4796-4806. ***Corresponding author** **Highlighted by the American Association of Cancer Research
4. **Yang, ES,** Nowsheen, S, Rahman, MA, Cook, R, Xia, F. Targeting BRCA1 localization to augment breast tumor susceptibility to poly(ADP-ribose) polymerase inhibition. Cancer Research, doi:10.1158/0008-5472.CAN-12-0934.
5. Nowsheen, S, Cooper, T, Stanley, JA, and **Yang, ES***. Synthetic lethal interactions between EGFR and PARP inhibition in human triple negative breast cancer cells. PLoS One 2012. 7(10): e46614. ***Corresponding author.**
6. Swindall, AF, Stanley, J, and **Yang, ES***. PARP-1: Friend or foe of DNA damage and repair in tumorigenesis? Cancers 2013. 5(3), 943-958. ***Corresponding author**
7. Wieglos, M and **Yang, ES***. Current clinical status of PARP inhibitors in cancer therapy. Pharmaceutical Patent Analyst 2013. In press. ***Corresponding author**

CONCLUSION: In summary, IR induces synthetic lethality with PARP inhibition in LNCaP prostate cancer cells. The mechanism is due to IR-mediated BRCA1 nuclear export and subsequent generation of an HDR defect. These results are dependent on p53 and CRM1. For tumors without wildtype p53, we have found that expression of a truncated BRCA1 (tr-BRCA1) can achieve similar results as IR, including BRCA1 nuclear export, inhibition of HDR, and synthetic lethality with PARPi in both p53 wildtype and mutated prostate cancer cells. Lastly, cytotoxicity to this regimen is correlated with increased accumulation of cells in the G2/M phase of the cell cycle as well as persistent DNA damage.

APPENDICES: My CV is appended.

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Date: October 1, 2013

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None

EDUCATION:

1997 – 1999 Doctorate of Medicine, Research Distinction
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1999 – 2003 Doctorate of Philosophy, Department of Molecular and Cellular Pharmacology
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1993 – 1996 Bachelor of Arts in Biology with honors, Russian Minor, Johns Hopkins University, Baltimore, MD

MILITARY SERVICE: N/A

LICENSURE: AL Medical License

BOARD CERTIFICATION:

USMLE Steps 1-3
Radiation Biology and Physics 2009
Clinical Radiation Oncology Written Boards 2010
Clinical Radiation Oncology Oral Boards 2011

POSTDOCTORAL TRAINING:

2010 LDR Brachytherapy Fellowship, Seattle Prostate Institute

2006 – 2010 Residency, Department of Radiation Oncology, Vanderbilt University School of Medicine, Nashville, TN
ABR Holman Research Scholar
Nucletron Prostate HDR Training Course 2009
Chief Resident 2009-2010

2005 – 2006 Internship, Department of Internal Medicine, Mount Sinai Medical Center, Miami Beach, FL

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2013 – Present, Scientist, Comprehensive Cancer Center, University of Alabama at Birmingham

2012 – Present, Guest Professor, Guangdong Medical College, Zhanjiang, Guangdong Province, People's Republic of China

2012 – 2013, ROAR Southeast Cancer Foundation Endowed Professor, Department of Radiation Oncology, University of Alabama at Birmingham

2010 – 2013, Assistant Professor, Departments of Radiation Oncology; Pharmacology and Toxicology; and Cell, Developmental, and Integrative Biology, University of Alabama at Birmingham

2010 – 2013, Associate Scientist, Comprehensive Cancer Center, University of Alabama at Birmingham

AWARDS/HONORS:

- Susan G Komen Foundation Career Catalyst Award 2013
- National Natural Science Foundation of China (NSFC) grant award 2012
- American Society for Radiation Oncology (ASTRO) Annual Meeting Basic Science Abstract Award 2012
- American Association for Cancer Research (AACR) – Genentech Career Development Award 2012
- Breast Cancer Research Foundation of Alabama Research Award 2012

- Mini-symposium speaker, 14th International Congress of Radiation Research, Warsaw, Poland — 2011
- John R. Durant Award for Excellence in Cancer Research — 2011
- Translational Scholar Award, Sidney Kimmel Foundation for Cancer Research — 2011
- Medical Research Award, Gabrielle's Angel Foundation for Cancer Research — 2011
- UAB CCTS/COCD Translational Science Pilot Award — 2011
- Fighting Children's Cancer Foundation Award — 2011
- Department of Defense (DOD) Physician Research Training Award — 2010
- UAB Breast SPORE Career Development Award — 2010
- American Society for Radiation Oncology (ASTRO) Annual Meeting Basic Science Abstract Award — 2010
- Best Poster Presentation Award, Vanderbilt University Research Forum 2010 — 2010
- American Brachytherapy Society Seattle Prostate Brachytherapy Fellowship Award — 2010
- 3rd place, Vanderbilt Ingram Cancer Center Research Retreat Poster Competition — 2010
- Chief Resident, Dept of Rad Onc Vanderbilt University — 2009
- Roentgen Resident Research Award — 2009
- 3rd place, Vanderbilt Ingram Cancer Center Research Retreat Poster Competition — 2009
- Elliot V. Newman Best Oral Presentation Award, Vanderbilt University Research Forum 2009 — 2009
- NIH LRP Award Recipient — 2008
- American Society for Radiation Oncology (ASTRO) Basic Science Travel Grant — 2008
- American Society for Radiation Oncology (ASTRO) Research Resident Seed Grant — 2008
- Radiological Society of North America (RSNA) Research & Education Foundation Grant — 2008
- Elliot V. Newman Best Oral Presentation Award, Vanderbilt University Research Forum 2008 — 2008
- Three microgrants from the Vanderbilt Institute for Clinical and Translational Research — 2008
- Chair Fund Recipient, Gordon Research Conference: Understanding the DNA Damage Response to Optimize Radiation Therapy — 2007
- Radiological Society of North America (RSNA) Research & Education Foundation Grant — 2007
- American Board of Radiology Holman Research Pathway — 2006
- Alpha Omega Alpha Medical Fraternity — 2005
- Award of Academic Merit, University of Miami School of Medicine — 2003
- Second Place, Biomedical Sciences, University of Miami Graduate School Research and Creativity Forum — 2003
- Travel Grant, University of Miami School of Medicine—The Medical Faculty Association Margaret Whelan Graduate Student Scholarship Fund — 2002

- Second Place, Best Research Award, University of Miami School of Medicine Medical Faculty Association — 2002
- First Place, Biomedical Sciences, University of Miami Graduate School Research and Creativity Forum — 2002
- Travel Grant, Annual Meeting of the Society for Basic Urological Research (SBUR) — 2000
- Travel Grant, NATO/FEBS Advanced Study Institute on Protein Modules in Cellular Signaling, National Science Foundation — 2000
- Predoctoral Fellowship, NIH/NIEHS — 2000
- Florida Medical Scholar — 1999
- Predoctoral Fellowship, NIH/NCBI — 1996
- Phi Beta Kappa — 1996
- Deans' List every semester, Johns Hopkins University — 1993–1996

PROFESSIONAL SOCIETIES/MEMBERSHIPS:

- American Society for Therapeutic Radiology and Oncology (ASTRO)
- American Society for Clinical Oncology (ASCO)
- American Association for Cancer Research (AACR)
- American Board of Radiology (ABR)
- Radiological Society of North America (RSNA)
- Radiation Research Society (RRS)
- American College of Radiation Oncology (ACRO)
- American Brachytherapy Society (ABS)
- Roentgen Society, Vanderbilt University
- Alpha Omega Alpha Medical Fraternity

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- Member, Clinical Trials Review Committee (CTRC) — 2013-
- Science, Education, and Program Development Committee, ASTRO — 2013-
- Research Grants Evaluation Committee, ASTRO — 2013-
- The Halifax Project – Broad-spectrum therapeutic design task force — 2013-
- Medical Scientist Training Program Advisory Committee, UAB — 2013-
- Head and neck cancer working group, Division of Cancer Treatment and Diagnosis, National Cancer Institute — 2013-
- Reviewer, UAB Radiation Oncology Intramural Pilot Grant Program — 2013-
- Auditor, Clinical Trials Quality Assurance Committee — 2012-
- Resident Curriculum Review Committee, UAB Radiation Oncology — 2012–
- Mock Board Examiner, Vanderbilt University Radiation Oncology — 2012–
- Translational Breast Cancer Research Consortium — 2010–
- Residency Admissions Committee, UAB Radiation Oncology — 2010–
- Founder & Chair, Vanderbilt Roentgen Society — 2009–
- Board of Directors, Vanderbilt Medical Alumni Association — 2010–
- Chief Resident, Vanderbilt University Radiation Oncology — 2009–2010
- Representative, House Staff Advisory Council — 2009–2010
- Co-Director, Eastern Student Research Forum (ESRF) sponsored by the American Medical Association — 1999–2000
- Registration Committee Chair for ESRF — 1998–1999

- Class of 2001 Treasurer, University of Miami School of Medicine 1997–1998
- Board of Intramural Athletics, Johns Hopkins University 1994–1996

UNIVERSITY ACTIVITIES:

- Careers in Oncology Student Interest Group, Faculty Advisor 2013-
- American Physician Scientist Association, UAB Guest speaker 2013
- UAB PREP Scholar Program mentor 2012-
- Summer Internship in Biomedical Science mentor 2012-
- GBS Winter Poster Session, Judge 2012-
- Urology Faculty Recruitment Interviewer 2012-
- Clinical and Translational Science Program mentor 2011-
- Surgical Oncology Faculty Recruitment Interviewer 2011-
- Medical Scientist Training Program (MSTP) Faculty Member 2011-
- Cancer Biology theme within the Graduate Biomedical Sciences Faculty Member 2011-
- Cell, Molecular, and Developmental Biology theme within the Graduate Biomedical Sciences Faculty Member 2011-
- Pathobiology and Molecular Medicine theme within the Graduate Biomedical Sciences Faculty Member 2011-
- Neuroscience theme within the Graduate Biomedical Sciences Faculty Member 2011-
- Post-doctoral research day, Judge, Cancer Biology 2011-
- ACS-Us Too Prostate Cancer Support Group 2011-
- Lung cancer working group, UAB-CCC 2011-
- Holman Research Pathway Mentor 2010-
- Residency applicant interviewer 2010-
- Translational Breast Cancer Research Consortium 2010-
- Breast cancer working group, UAB-CCC 2010-
- Head & neck cancer working group, UAB-CCC 2010-
- Head and neck cancer “Think Tank” 2010-
- Genitourinary cancer working group, UAB-CCC 2010-
- Experimental Therapeutics, UAB-CCC 2010-

EDITORIAL BOARD MEMBERSHIPS:

EDITORIAL BOARD:

- Editorial board member, *Journal of Tumor*
- Guest Editor, *Breast Diseases: A Year Book Quarterly*

PEER REVIEWER:

- *Cancer Research*
- *Molecular Cancer Therapeutics*
- *PLOS One*
- *Cancer Biology and Therapy*
- *Current Cancer Drug Targets*
- *Frontiers in Radiation Oncology*
- *Cancer Biotherapy and Radiopharmaceuticals*
- *Pharmaceutics*

- *Current Molecular Medicine*
- *Cancer Letters*
- *Head and Neck*
- *Frontiers in Medicine*
- *J Cancer Science and Therapy*
- *International Journal of Radiation Biology*
- *Tumor Biology*

MAJOR RESEARCH INTERESTS: My laboratory interests focus on the targeting of DNA repair pathways to improve the therapeutic ratio. Specifically, we can enhance tumor susceptibility to DNA damage by novel combinations of targeted agents. Additionally, we aim to protect normal brain by augmenting DNA repair pathways.

TEACHING EXPERIENCE:

TEACHING:

- Resident Lecturer, Radiation Biology, University of Alabama-Birmingham 2012-
- Course co-director, Translational Medicine, University of Alabama-Birmingham 2012-
- Lecturer, Carcinogenesis: DNA repair/Genome stability University of Alabama-Birmingham 2012
- Lecturer, GBS775: Principles of Radiotherapy, University of Alabama-Birmingham 2011
- Lecturer, GBS775: Hormone Therapy Prostate Cancer, University of Alabama-Birmingham 2011
- Radiobiology Review, DNA repair pathways, University of Alabama-Birmingham 2011
- Molecular Radiation Oncology Lecture Series, University of Alabama-Birmingham 2010
- Clinical Oncology Lecture Series for Vanderbilt University Medical Center Medical Physics Program 2006–2010

MENTORSHIP/TRAINING:

Research

- Rebecca Arend, MD, Gyn-Onc Fellow
- Alice Weaver, MD/PhD Student, Dissertation mentor, Cancer Biology Program
- Amanda Swindall, PhD, Post-doctoral Fellow
- Marcela Rodriguez, UAB PREP Scholar Program
- Tanu Patel, Summer Internship Biomedical Science Program
- Amber L. Guidry, PhD student, Dissertation committee member, Pathobiology and Molecular Medicine Program
- Monica Wieglos, PhD student, Dissertation mentor, Cancer Biology Program
- Jennifer Stanley, MD/PhD student, Dissertation mentor, Cancer Biology Program
- Monjri Shah, MD, Gyn-Onc Fellow
- Angela Ziebarth, MD, Gyn-Oncology Fellow
- Caroline Mills, PhD, Post-doctoral fellow
- Alex Whitley, MD, PhD, Radiation Oncology Resident, Research mentor, American Board of Radiology Holman Research Pathway

- Lisa Klepczyk, MD, Radiation Oncology Resident, Mentor, Clinical and Translational Science Training Program
- Aleksander Dragovic, MD, Radiation Oncology Resident
- Somaira Nowsheen, MS, MD/PhD Student Mayo
- Joshua Jackson, rotation student, Cancer Biology Program
- Karla Mihalak, 2nd year graduate student, lab rotation, University of Miami School of Medicine.
- Drew Everhart, 2nd year graduate student, lab rotation, University of Miami School of Medicine.

Clinical Resident Rotations

- Jennifer Hung, MD
- John Stewart, MD
- Aleksander Dragovic, MD
- Marcus Wagner, MD
- Lisa Klepczyk, MD
- Grant Clark, MD
- Alexander Whitley, MD, PhD
- Markus Bredel, MD, PhD
- Craig Baiden, MD
- Javier Lopez, MD
- Robert Taylor, MD, PhD
- Jonathan Thompson, MD

Mentee Honors and Awards

- Somaira Nowsheen – Poster Discussion, ASTRO annual meeting 2012
- Monjri Shah, MD – Featured poster, Society Gyn-Oncology Annual Meeting 2012
- Alice Weaver – Best Poster (1st place), UAB Medical Student Research Day
- Jennifer Stanley - 1st place, UAB Graduate School Research Day 2013
- Jennifer Stanley - 3rd place, UAB Graduate School Research Day 2012
- Tanu Patel – 3rd place, UAB Summer Research Expo
- Alex Whitley, MD, PhD – ABR Holman Research Pathway
- Alex Whitley, MD, PhD – Roentgen Research Resident Award
- Alex Whitley, MD, PhD – Bo Johnson Memorial Foundation Pilot Research Grant
- Alex Whitley, MD, PhD – NIH LRP Awardee
- Alex Whitley, MD, PhD – Oral Presentation, ASTRO annual meeting 2012
- Lisa Klepczyk, MD – Oral Presentation, ASTRO annual meeting 2011
- Lisa Klepczyk, MD – Radiation Oncology Intramural Pilot Grant Award 2012

MAJOR LECTURES AND VISITING PROFESSORSHIPS:

- Visiting Professor, Guangdong Medical College Zhanjiang, Guangdong Province, People's Republic of China — 2013
- Visiting Professor, Vanderbilt University, Nashville, TN — 2013
- Visiting Professor, Washington University, St Louis, MO — 2012
- Invited speaker, Vanderbilt University Research Retreat — 2012
- Clinical trial concept speaker, HER2 positive Breast Cancer Working Group, Translational Breast Cancer Research Consortium, Hollywood, FL — 2012

- Clinical trial concept speaker, Triple Negative Breast Cancer Working Group, Translational Breast Cancer Research Consortium, Hollywood, FL 2012
- Guest Professor, Guangdong Medical College, People's Republic of China 2012
- Mini-symposium speaker, 14th International Congress of Radiation Research, Warsaw, Poland 2011
- Invited speaker, UAB Comprehensive Cancer Center Research Retreat 2011
- Mini-symposium speaker, Annual Meeting of the Radiation Research Society, Maui, Hawaii 2010
- Invited lecturer, Mid-South Society of Radiation Therapists Spring Conference 2006

CLINICAL PROTOCOLS:

ACTIVE:

M10-897: A Randomized, Double-Blind, Phase 2, Dose-Ranging Study to Evaluate the Safety and Efficacy of Veliparib and Whole Brain Radiation Therapy Versus Placebo and Whole Brain Radiation Therapy in Subjects with Brain Metastases from Non-Small Cell Lung Cancer
Role: Institutional Principal Investigator

UAB X101214005: A retrospective analysis of DNA repair and EGFR pathway molecular markers in HER2/Neu positive breast cancer patients in order to predict response to PARP inhibition
Role: Principal Investigator

UAB X110504004: Pilot study of the molecular determinants of cellular susceptibility to PARP inhibition in an ex-vivo model of human cervical cancer
Role: Principal Investigator

UAB X1219: Molecular determinants of cellular susceptibility to PARP inhibition in an ex-vivo model of human cholangiocarcinoma
Role: Prinicipal Investigator

PENDING (Investigator Initiated Studies):

An open label pilot study evaluating the tolerability and efficacy of combination lapatinib and veliparib in patients with metastatic or recurrent triple negative breast cancer
Role: co-Principal Investigator

GRANT SUPPORT:

ACTIVE:

Career Catalyst Award (PI: YANG) 7/1/13 – 6/30/17 2.4Cal Months
Susan G. Komen Foundation $450,000
DNA repair independent mechanisms of HER2+ tumor sensitivity to PARP inhibition
The major goals of the project are to find the mechanisms by which HER2+ tumors are sensitive to PARP inhibition despite being DNA repair proficient.
Role: Principal Investigator

Investigator Initiated Clinical Study (PI: Forero) 7/1/13 – 6/31/15 0 Cal Months
Scariot Foundation $100,000
Lapatinib/Veliparib in triple negative breast cancer
Major goal is to perform an open label pilot study of combination lapatinib/veliparib in patients with metastatic or recurrent triple negative breast cancer.
Role: Co-Principal Investigator

Investigator Initiated Preclinical Study (PI: YANG) 6/1/13 – 3/31/14 1.2Cal Months
Eli-Lilly and Company $163,953
Confidential title
Role: Principal Investigator

Investigator Initiated Preclinical Study (PI:Bonner) 7/1/13 – 6/30/14 0 Cal Months
Bristol Myers Squibb $45,000
Confidential title
Role: Co-Principal Investigator

Investigator Initiated Preclinical Study (PI: YANG) 2/1/13 – 1/31/14 0 Cal Months
Lewis-Moseley Award, Southeast Cancer Foundation $100,000
PARP inhibitors in ovarian cancer
The major goals of the project are to find and predict novel combinations of targeted therapies that can synergize with PARP inhibition in ovarian cancers.
Role: Principal Investigator

Collaborative Research Grant (PI: Li) 1/1/13 – 12/31/13 0 Cal Months
National Natural Science Foundation of China (NSFC)
BRCA1 modulates choice of precise and error-prone NHEJ subpathway
The major goals of the project are to understand the mechanisms by which BRCA1 regulates the choice by which cells repair DNA damage.
Role: Co-investigator

Research Grant (PI: Li) 10/1/12 – 09/30/14 0 Cal Months
National Science Foundation of Guangdong Province, China
BRCA1 roles in the NHEJ pathway
The major goals of this project are to investigate the roles that BRCA1 plays in nonhomologous end joining DNA repair.
Role: Co-investigator

Career Development Award (PI: YANG) 7/1/12 – 6/30/14 0.36 Cal Months
American Association for Cancer Research $100,000
Genentech BioOncology

HER2 overexpression confers susceptibility to PARP inhibition
The major goal of the project is to explore the mechanism by which HER2+ breast tumors are susceptible to PARP inhibition alone.
Role: Principal Investigator

Medical Research Award (PI: YANG) 2/1/11 – 1/31/14 0.6 Cal Months
Gabrielle's Angel Foundation for Cancer Research $225,000
Mechanisms by which GSK3β inhibition enhances nonhomologous end-joining repair of IR-induced double strand breaks
The major goals of the project are to investigate the mechanisms by which GSK3β inhibition enhances nonhomologous end-joining repair in irradiated hippocampal neurons and to determine whether this is dependent on the tumor suppressor p53
Role: Principal Investigator

Translational Science Scholar Award (PI: YANG) 7/1/11 – 6/30/13 1.2 Cal Months
Sidney Kimmel Foundation for Cancer Research $200,000
Can cetuximab induce synthetic lethality with PARP inhibition in head and neck cancer?
The major goal of the project is to determine the mechanisms by which cetuximab induces synthetic lethality with PARP inhibition.
Role: Principal Investigator

Bo Johnson Memorial Foundation (PI: YANG) 11/1/11 – 10/31/13
Pilot Project Grant for Esophageal Cancer $50,000
Targeting EGFR Pathways to induce Synthetic Lethality of Esophageal Tumors to PARP Inhibition
The major goal of the project is to target EGFR to render esophageal tumors susceptible to PARP inhibition
Mentored grant for Alexander Whitley, MD, PhD
Role: Principal Investigator/Mentor

Physician Research Training Award (PI: YANG) 8/1/10 – 7/31/13 6.6 Cal Months
PC094457, Department of Defense $413,949
Targeting homology-directed recombinational repair (HR) of chromosomal breaks to sensitize prostate cancer cells to poly (ADP-Ribose) polymerase (PARP) inhibition
The major goals of the project are to render prostate cancer cells with intact HR susceptible to PARP inhibition with radiation or dominant negative BRCA1 peptide.
Role: Principal Investigator

Pilot Grant Award (PI: YANG) 10/1/12 – 11/30/13 0 Cal Months
Breast Cancer Research Foundation of Alabama $25,000
DNA repair independent mechanism of PARPi susceptibility
The major goal of the project is to determine the DNA repair independent mechanisms by which tumors are susceptible to PARP inhibition
Role: Principal Investigator

UAB X101214005 (PI: YANG) 5/15/2012 – Present
UAB Radiation Oncology $5,000
A retrospective analysis of DNA repair and EGFR pathway molecular markers in HER2/Neu positive breast cancer patients in order to predict response to PARP inhibition
Mentored intramural grant for Lisa Klepczyk, MD
Role: Principal Investigator/Mentor

UAB X1219 (PI: JACOB) 5/1/2012 – Present
UAB Radiation Oncology $3,500
Molecular determinants of cellular susceptibility to PARP inhibition in an ex-vivo model of human cholangiocarcinoma
Role: Co-Prinicipal Investigator

UAB X110504004 (PI: YANG) 3/1/2012 – Present
UAB Radiation Oncology $8,500
Pilot study of the molecular determinants of cellular susceptibility to PARP inhibition in an ex-vivo model of human cervical cancer
Mentored intramural grant for Aleksander Dragovic, MD
Role: Principal Investigator/Mentor

COMPLETED:
Career Development Award (PI: JACOB) 10/1/11 – 9/30/12
UAB/NIH PANCREATIC SPORE $50,000
Radiosensitization and SPARC interactions of ABI-007 in pancreatic cancer
The major goal of this project is to assess interactions and molecular determinants of the nano-albumin-bound paclitaxel (Abraxane, or ABI-007) with the SPARC protein that can determine response of tumors to Abraxane, radiation, or other chemotherapies.
Role: Co-Investigator

Career Development Award (PI: YANG) 9/1/10 – 8/31/12
UAB/NIH BREAST SPORE $100,000
Targeting HER pathways to render triple negative breast cancer cells susceptible to PARP inhibition
The major goal of the project is to convert triple negative breast tumor susceptibility to PARP inhibition by targeting HER pathways with lapatinib.
Role: Principal Investigator

Translational Research Pilot Award (PI: YANG) 5/1/11 – 7/31/12
UAB Center for Clinical and Translational Science $60,000
Targeting EGFR pathways to induce synthetic lethality of head and neck tumors to poly (ADP-Ribose) polymerase inhibitors (PARPi)
The major goal of the project is to induce synthetic lethality using EGFR and PARP inhibition *in vivo* in mice bearing orthotopically implanted head and neck tumor xenografts.
Role: Principal Investigator

IMPACT Award (PI: YANG) 7/1/10 – 6/30/12
UAB School of Medicine $150,000
This award supports biomedical research aligned with the research priorities of UAB, including the UAB School of Medicine's research strategic plan, and is used for recruiting and setup of Dr. Yang's laboratory.
Role: Principal Investigator

Pilot Grant Award (PI: YANG) 2/1/2011
Fighting Children's Cancer Foundation $2500
Funds were used to generate preliminary data investigating mechanisms of neuroprotection by GSK3 inhibition
Role: Principal Investigator

RR0813 (PI: YANG) 7/1/08 – 12/31/09
Radiological Society of North America Research and Education Foundation
Neuroprotection via enhanced repair of radiation-induced DNA damage by GSK3 inhibitors
Role: Principal Investigator

Resident Research Grant (PI: YANG) 7/1/08 – 12/31/09
American Society for Therapeutic Radiology and Oncology
Targeting homologous recombination repair to sensitize cancer cells to PARP inhibitors
Role: Principal Investigator

Microgrant, CTSA UL1RR024975 (PI: YANG) 9/1/08 – 3/31/09
Vanderbilt Institute for Clinical and Translational Research
GSK3 inhibition and DNA repair
Role: Principal Investigator

RR0725 (PI: YANG) 7/1/07 – 12/31/08
Radiological Society of North America Research and Education Foundation
Role of lithium and specific GSK-3 inhibitors in neural protection during cranial irradiation
Role: Principal Investigator

Microgrant, CTSA UL1RR024975 (PI: YANG) 3/1/08 – 11/30/08
Vanderbilt Institute for Clinical and Translational Research
Targeting BRCA1 location to enhance prostate cancer sensitivity to PARP inhibitors
Role: Principal Investigator

Microgrant, CTSA UL1RR024975 (PI: YANG) 3/1/08 – 11/30/08
Vanderbilt Institute for Clinical and Translational Research
BRCA1 subcellular localization and lung cancer response to Tarceva
Role: Principal Investigator

5F30ES005910-04 (PI: YANG) 4/1/02 – 6/30/05
National Institute of Environmental Health Sciences, National Institute of Health
NRSA F30 Fellowship Grant
Vitamin D mediated growth inhibition of prostate cancer cells
Role: Principal Investigator

OTHER:

BIBLIOGRAPHY:

MANUSCRIPTS:

Already Published:

1. De Marzo, AM, Marchi, VL, **Yang, ES**, Veeraswamy, R, Lin, X, and Nelson, WG. Abnormal regulation of DNA methyltransferase expression during colorectal carcinogenesis. *Cancer Research* 1999. 59: 3855 - 3860.

2. **Yang, ES**, Maiorino, CA, Roos, BA, Knight, SR, and Burnstein, KL. 1,25-$(OH)_2$ vitamin D_3-mediated growth inhibition of an androgen ablated prostate cancer cell model involves the cyclin-dependent kinase inhibitor p27. *Molecular & Cellular Endocrinology* 2002. 186(1): 69 – 79.

3. **Yang, ES** and Burnstein, KL. Vitamin D inhibits G1 to S progression in LNCaP prostate cancer cells through $p27^{Kip1}$ stabilization and Cdk2 mislocalization to the cytoplasm. *Journal of Biological Chemistry* 2003. 278: 46847 – 46868.

4. Knight-Krajewski, S, Welsh, CF, Liu, YQ, Lyons, L, Faysal, J, **Yang, ES**, and Burnstein, KL. Deregulation of the Rho GTPase, Rac1, suppresses cyclin-dependent kinase inhibitor $p21^{CIP1}$ in androgen-independent human prostate cancer cells. *Oncogene* 2004. 23: 5513 - 5522.

5. **Yang, ES***, Moretti, L*, Kim, KW, Lu, B. Autophagy signaling in cancer and its role as a novel target to enhance cancer therapy. *Drug Resistance Updates* 2007. 10: 135 – 143. *co-first authors.

6. Jaboin, JJ, Shinohara, ET, Moretti, L, **Yang, ES**, Kaminski, JM, Lu, B. The role of mTOR inhibition in augmenting radiation induced autophagy. *Tech Cancer Research & Treatment* 2007. 6(5): 433 – 448.

7. Li, L, Wang, H*, **Yang, ES***, Arteaga, CL, Xia, F. Erlotinib attenuates homologous recombinational repair of chromosomal breaks in human breast cancer cells. *Cancer Research* 2008. 68(22): 9141 – 9146. *co-authors.

8. **Yang, ES***, Wang, H*, Jiang, G, Nowsheen, S, Fu, A, Hallahan, DE, Xia, F. Lithium-mediated protection of hippocampal cells involves enhancement of DNA-PK dependent repair in mice. *J Clinical Investigation* 2009. 119(5): 1124 – 1135. *co-first authors.

9. **Yang, ES**, Murphy, BM, Chung, CH, Netterville, JL, Burkey, BB, Gilbert, J, Yarbrough, WG, Sinard, R, Cmelak, AJ. Evolution of clinical trials in head and neck cancer. *Critical Reviews in Oncology/Hematology* 2009. 71: 29 – 42.

10. **Yang, ES***, Wu, FY*, Willey, CD, Atkinson, JB, Ely, K, Garrett, G, Cmelak, AJ. Refractory lympho-epithelial carcinoma of the nasopharynx: A case report illustrating a protracted clinical course. *Head and Neck Oncology* 2009. 1:18. *co-first authors

11. Pawlowski, JM, **Yang, ES,** Malcolm, AW, Coffey, CW, Ding, GX. Reduction of dose delivered to organs-at-risk in prostate cancer patients via image-guided radiation therapy (IGRT). *IJROBP* 2010. 76: 924 – 934.

12. **Yang, ES** and Xia, F. DNA damage-induced BRCA1 shuttling. *FEBS Journal* 2010. 277: 3079 – 3085.

13. **Yang, ES***, Wang, H*, Jiang, J, Nowsheen, S, Feng, Z, Xia, F. DNA damage-induced cytotoxicity is dissociated from BRCA1's function in DNA repair but is dependent on its cytosolic accumuation. *Cancer Research* 2010. 70: 6258 – 6267. *co-first authors**.**

14. **Yang, ES,** Nowsheen, S, Thotala, D, Hallahan, DE, Xia, F. GSK3β inhibition enhances repair of double strand breaks in irradiated hippocampal neurons. *Neuro-Oncology* 2011. 13: 459 – 470.

15. Bonner, JA, Willey, CD, **Yang, ES**, Dobelbower, MC, Sanford, LL, Bright, SJ, Buchsbaum, DJ, Raisch, KP. Treatment of Small Cell Lung Cancer with TRA-8 in Combination with Cisplatin and Radiation. *Radiother Oncol* 2011. doi:10.1016/j.radonc.2011.05.083.

16. Deeley, MA, Chen, A, Datteri, R, Noble, J, Cmelak, A, Donnelly, E, Malcolm, A, Moretti, L, Jaboin, J, Niermann, K, **Yang, ES**, Yu, DS, Yei, F, Koyama, T, Ding, GX, Dawant, BM. Comparison of manual and automatic segmentation methods for brain structures in the presence of space-occupying lesions: a multi-expert study. *Phys Med Biol* 2011. 56:4557-77.

17. Nowsheen, S, Bonner, JA, **Yang, ES**. The poly (ADP-Ribose) polymerase inhibitor ABT-888 reduces radiation-induced nuclear EGFR and augments head and neck tumor response to radiotherapy. *Radiother Oncol* 2011. 99: 331 – 338.

18. Nowsheen, S, Trummell, H, Whitley, AC, Dobelbower, MC, LoBuglio, AF, Bonner, JA, **Yang, ES**. Cetuximab induces synthetic lethality with poly (ADP-Ribose) polymerase inhibition in head and neck cancer. *PLOS One*, 2011. 6: e24148.

19. Bonner, JA, **Yang, ES**, Trummell, HQ, Nowsheen, S, Willey, CD, Raisch, KP. Inhibition of STAT-3 results in greater cetuximab sensitivity in head and neck squamous cell carcinoma. *Radiother Oncol* 2011. 99: 339 – 343.

20. **Yang, ES*,** Jiang, J*, Nowsheen, S, Wang, H, Wang, T, Wang, Y, Billheimer, D, Chakravarthy, AB, Brown, M, Haffty, B, Xia, F. p53-dependent BRCA1 nuclear export controls cellular susceptibility to DNA damage. *Cancer Research* 2011. 71: 5546 – 5557. *co-first authors.

21. Mills, CN, Nowsheen, S, Bonner, JA, **Yang, ES.** Emerging roles of glycogen synthase kinase 3 in the treatment of brain tumors. *Front Mol Neurosci* 2011. 4: 47.

22. Nowsheen, S, Whitley, AC, **Yang, ES**. Biomarkers to assess the targeting of DNA repair pathways to augment tumor response to therapy. *Current Molecular Medicine* 2012. 12(6): 788-803.

23. Jarboe, JS, Anderson, JC, Duarte, CW, Mehta, T, Nowsheen, S, Hicks, PH, Whitley, AC, Rohrbach, TD, McCubrey, RO, Chiu, S, Burleson, TR, Bonner, JA, Gillespie, GY, **Yang, ES**, Willey, CD. MARCKS Regulates Growth, Radiation Sensitivity and is

a Novel Prognostic Factor for Glioma. *Clin Cancer Res* 2012. 18(11): 3030-41.

24. Jarboe, JS, Jaboin, JJ, Anderson, JC, Nowsheen, S, Stanley, JA, Ruijtenbeek, R, Tu, T, Hallahan, DE, **Yang, ES,** Bonner, JA, Willey, CD. Kinomic profiling approach identifies Trk as a novel radiation modulator. *Radiother Oncol 2012.* 103(3): 380-7.

25. Nowsheen, S, Aziz, K, Tran, PT, Gorgoulis, VG, **Yang, ES**, Georgakilas, AG. Epigenetic inactivation of DNA repair in breast cancer. *Cancer Letters 2012.* PMID: 22634493.

26. Nowsheen, S and **Yang, ES**. The intersection between DNA damage response and the apoptotic pathways. *Experimental Oncology* 2012. 34(3): 243-254.

27. McDonald, A, Bishop, JM, Dobelbower, MC, Kim, RY, **Yang, ES,** Smith, H, Wu, X, Fiveash, JB. Hypofractionated prostate radiotherapy with or without conventionally fractionated nodal irradiation: clinical toxicity observations and retrospective daily dosimetry. *Prostate Cancer* 2012: 546794.

28. Nowsheen, S, Cooper, T, Bonner, JA, LoBuglio, AF, **Yang, ES**. HER2 overexpression renders human breast cancers sensitive to PARP inhibition independently of any defect in homologous recombination DNA repair. *Cancer Research* 2012. 72(18): 4796-4806. ***Highlighted by the American Association of Cancer Research*

29. **Yang, ES**, Nowsheen, S, Rahman, MA, Cook, R, Xia, F. Targeting BRCA1 localization to augment breast tumor susceptibility to poly(ADP-ribose) polymerase inhibition. *Cancer Research,* doi:10.1158/0008-5472.CAN-12-0934.

30. Nowsheen, S, Cooper, T, Stanley, JA, and **Yang, ES.** Synthetic lethal interactions between EGFR and PARP inhibition in human triple negative breast cancer cells. *PLoS One* 2012. 7(10): e46614.

31. Nowsheen, S, Xia, F, and **Yang, ES**. Assaying DNA damage in hippocampal neurons using the comet assay. *Journal of Visualized Experiments* 2012. (70): e50049, doi:10.3791/50049.

32. Ziebarth, A, Nowsheen, S, Steg, AD, Shah, MM, Dobin, ZC, Han, H-D, Lopez-Berestein, G, Sood, AK, Conner, MB, **Yang, ES**, Landen, CN. Endoglin (CD105) contributes to platinum resistance and is a target for tumor-specific therapy in epithelial ovarian cancer. *Clinical Cancer Research* 2013. 19(1): 1-13.

33. Jiang, G, Plo, I, Wang, T, Rahman, M, Cho, JH, **Yang, ES**, Lopez, BS, Xia, F. BRCA1-Ku80 interaction enhances end-joining fidelity of chromosomal double-strand breaks in G1 phase of the cell cycle. *J Biol Chem* 2013. 288(13): 8966-8976.

34. Deeley, MA, Chen, A, Datteri, RD, Noble, J, Cmelak, A, Donnelly, E, Malcolm, A, Moretti, L, Jaboin, J, Niermann, K, **Yang, ES,** Yu, DS, Dawant, BM. Segmentation editing improves efficiency while reducing inter-expert variation and maintaining accuracy for normal brain tissues in the presence of space-occupying lesions. *Phys Med Biol* 2013. 58(12): 4071-4097.

35. Swindall, AF, Stanley, J, and **Yang, ES.** PARP-1: Friend or foe of DNA damage and repair in tumorigenesis? *Cancers* 2013. 5(3), 943-958.

36. Wieglos, M and **Yang, ES.** Current clinical status of PARP inhibitors in cancer therapy. *Pharmaceutical Patent Analyst* 2013. In press.

In revision:

Submitted:

37. Gebhardt, BJ, McDonald, AM, Bae, S, Singh, KP, Jacob, R, Dobelbower, MC, Kim, RY, **Yang, ES**, Fiveash, JB. Prognostic factors for salvage radiotherapy with an analysis of intra-treatment PSA kinetics.

38. Weaver, AN and Yang, ES. Beyond DNA repair: The additional functions of PARP. *Frontiers in Oncology* – invited expert review.

BOOK CHAPTERS:

1. Moretti, L, **Yang, ES**, Hallahan, DE, Lu, B. Lithium as a differential radioprotector following cranial irradiation. In *CURED II: Late Effects of Cancer Treatment on Normal Tissues (LENT)*. Edited by R. Rubin, L.S. Constine, L.B. Marks, and P. Okunieff. Springer: New York, 2008.

2. Ding, G., **Yang, E.S.**, Niermann, K., Xia, F. & Cmelak, A.J. MRI in Radiation Therapy Planning. In Quantitative MRI in Cancer (eds. Yankeelov, T.E., Pickens, D.R. & Price, R.R.) 265-276 (CRC Press, Taylor & Francis Group, New York, 2012).

3. Nowsheen, S and **Yang, ES**. Staying a step ahead of cancer. In *Cancer Prevention – From Mechanisms to Translational Benefit.* Edited by A. Georgakilas. InTech, 2012.

COMMENTARIES:

1. **Yang, ES** and Chakravarthy, AB. Commentary on "Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence," *IJROBP* (2008) 72: 1456 – 1464. In Breast Diseases: A Year Book Quarterly, volume 20. E Singletary and TA Buchholz, Eds. Mosby, Inc.

2. **Yang, ES** and Chakravarthy, AB. Commentary on "Regional nodal recurrence after breast conservation treatment with radiotherapy for women with early-stage breast carcinoma," *IJROBP* (2009) 73: 1475 – 1481. In Breast Diseases: A Year Book Quarterly, volume 20n2. E Singletary and TA Buchholz, Eds. Mosby, Inc

SELECTED PUBLISHED ABSTRACTS/POSTER EXHIBITS (from over 40):

1. **Yang, ES**, David-Beabes, G, Veeraswamy, R, Brooks, JD, and Nelson, WG. Expression of Human 5-methylcytosine DNA Methyltransferase in Human Prostate, Prostate Cancer, and the Prostate Cancer Cell Lines. Johns Hopkins University School of Medicine, Baltimore, MD. *Proceedings of the American Association for Cancer Research, 1997.*

2. **Yang, ES**, Iida, N, and Bourguignon, L. Novel CD44 Splice Variants in Human Ovarian Cancer. Department of Anatomy and Cell Biology, University of Miami

School of Medicine, Miami, FL. *American Medical Association's Eastern Student Research Forum, 1998.*

3. **Yang, ES**, Maiorino, CA, and Burnstein, KL. Antiproliferative Effects of 1,25-$(OH)_2$ Vitamin D_3 in an Androgen Ablated Prostate Cancer Cell Model. Department of Molecular and Cellular Pharmacology, University of Miami School of Medicine, Miami, FL. *Endocrine Society, March 2000; NATO/FEBS Advanced Study Institute on Protein Modules in Cellular Signalling, August 2000; Society of Basic Urological Research, November 2000.*

4. **Yang, ES** and Burnstein, KL. 1,25-$(OH)_2$ Vitamin D_3-Mediated Upregulation of the Cyclin Dependent Kinase Inhibitor p27Kip1 May Involve Decreased Nuclear Import. Department of Molecular and Cellular Pharmacology, University of Miami School of Medicine, Miami, FL. *University of Miami Graduate School Research and Creativity Forum, March 2002; Annual Zubrod Memorial Lectureship and Poster Session, June 2002.*

5. **Yang, ES** and Burnstein, KL. 1,25-$(OH)_2$ vitamin D_3-mediated upregulation of $p27^{kip1}$ in LNCaP cells involves decreased $p27^{kip1}$ degradation and correlates with decreased nuclear localization of cyclin-dependent kinase 2. Department of Molecular and Cellular Pharmacology, University of Miami School of Medicine. *University of Miami Graduate School Research and Creativity Forum, March 2003; Proceedings of the American Association for Cancer Research, July 2003.*

6. **Yang, ES,** Lu, B, and Hallahan, DE. Lithium-mediated neuroprotection during cranial irradiation: A phase I trial. Department of Radiation Oncology, Vanderbilt University Medical Center. *Proceedings of the American Society of Radiation Oncology, October 2007.*

7. **Yang, ES**, Wang, H, Hallahan, DE, Xia, F. Lithium-mediated protection of hippocampal cells involves enhancement of DNA-PK dependent nonhomologous end joining of chromosomal breaks. Department of Radiation Oncology, Vanderbilt University Medical Center. *Chair Fund Award, Gordon Research Conference: Understanding the DNA damage response to optimize radiation therapy, January 2008.*

8. **Yang, ES**, Wang, H, Li, L, Xia, F. Dissociation of BRCA1's DNA repair function from DNA damage-induced cytotoxicity: A dependence on BRCA1 localization. Department of Radiation Oncology, Vanderbilt University Medical Center. *Proceedings of the American Society of Radiation Oncology, September 2008.*

9. **Yang, ES**, Wang, H, Nam, EA, Wang, Y, Billheimer, D, Chakravarthy, AB, Brown, M, Haffty, B, Xia, F. Can sporadic breast cancers with genetically wild-type BRCA1 behave phenotypically like BRCA1-associated breast tumors? Department of Radiation Oncology, Vanderbilt University Medical Center. *Proceedings of the American Society of Radiation Oncology, November 2009.*

10. **Yang, ES,** Nowsheen, S, Xia, F. Targeting BRCA1 localization to convert tumor cell susceptibility to PARP inhibition. Department of Radiation Oncology, University of

Alabama-Birmingham. *Proceedings of the American Society of Therapeutic Radiation Oncology, November 2010.*

11. Klepczyk, L, Nowsheen, S, Xia, F, **Yang, ES**. BRCA1 Nuclear Export Sensitizes Prostate Cancer Cells to Poly (ADP-ribose) Polymerase-1 (PARP1) Inhibition via the CRM1/exportin Pathway. Department of Radiation Oncology, University of Alabama-Birmingham. *Proceedings of the American Society of Radiation Oncology, October 2011.*

12. Fiveash J, Bishop JM, Jacob R, Kim RY, Dobelbower MC, **Yang ES**, McDonald A, Smith H, Wu X: Daily Rectal Dosimetry in Patients with Late Grade 2 or Greater Rectal Toxicity after Hypofractionated Image Guided Radiation Therapy for Prostate Cancer. *Proceedings of the American Society of Radiation Oncology, October 2011.*

13. Whitley AC, **Yang ES**, Shen S, Spencer S, Minnich DJ, Dobelbower MC. Comparison of respiratory gate triggered kilovoltage (kV) portal images (GTPI) versus kV cone-beam computed tomography images (CBCT) for patient alignment and verification thoracic stereotactic body radiotherapy (SBRT) patients with implanted fiducial markers. *Proceedings of the American Society of Radiation Oncology, October 2011.*

14. Whitley, AC, Nowsheen, S, Cooper, T, Trummel, H, LoBuglio, AF, Bonner, JA, **Yang, ES.** Cetuximab induces synthetic lethality with the poly(ADP-Ribose) polymerase inhibitor ABT-888 in head and neck cancer. *Gordon Research Conference, March 2012.*

15. Whitley, AC, Nowsheen, S, Cooper, T, LoBuglio, AF, Bonner, JA, **Yang, ES.** Synthetic lethal interactions between EGFR and PARP inhibition in multiple tumor types. *Proceedings of the American Association for Cancer Research, April 2012.*

16. **Yang, ES**, Nowsheen, S, Cooper, T, Bonner, JA, LoBuglio, AF. Human HER2+ breast tumor susceptibility to PARP inhibitors independent of a homologous recombination repair defect. *Proceedings of the American Society of Clinical Oncology, June 2012.*

17. Nowsheen, S, Cooper, T, LoBuglio, AF, Bonner, JA, **Yang, ES.** Synthetic lethal interactions between EGFR and PARP inhibition in triple negative breast cancer. ***Poster discussion.** *Proceedings of the American Society of Radiation Oncology, October 2012.*

18. Whitley, AC, Jackson, J, Trummel, H, Bonner, JA, **Yang, ES**. Erlotinib induces synthetic lethality with the poly (ADP-Ribose) polymerase (PARP) inhibitor ABT-888 in esophageal cancer. *Proceedings of the American Society of Radiation Oncology, October 2012.*

19. **Yang, ES**, Nowsheen, S, Cooper, T, Bonner, JA, LoBuglio, AF. Human HER2+ breast tumor susceptibility to PARP inhibitors independent of a homologous recombination repair defect. *Proceedings of the American Society of Radiation Oncology, October 2012.*

20. Bonner, JA, Trummell, H, Nowsheen, S, **Yang, ES**. The role of STAT-3 in cetuximab-induced radiosensitization in head and neck cancer cells. *Proceedings of the American Society of Radiation Oncology, October 2012.*

ORAL PRESENTATIONS/INVITED TALKS:

1. Wang, Z, **Yang, ES,** and Burnstein, KL. Vitamin D3 Inhibits Cancer Cell Proliferation through Nuclear Exclusion and Decreased Activity of Cyclin-Dependent Kinase 2. *Podium presentation at Keystone Symposia: Hormonal regulation of tumorigenesis, February 2005.*

2. **Yang, ES.** Early Stage Breast Cancer**.** *Mid-South Society of Radiation Therapists Spring Conference, May 2006.*

3. **Yang, ES,** Wang, H, Jiang, G, Hallahan, DE, Xia, F. Lithium-mediated protection of hippocampal cells involves enhancement of DNA-PK dependent nonhomologous end joining of chromosomal breaks. *Vanderbilt University Research Forum, April 2008.* Elliot V. Newman Best Oral Presentation Award.

4. **Yang, ES**, Wang, H, Li, L, Xia, F. Dissociation of BRCA1's DNA repair function from DNA damage-induced cytotoxicity: A dependence on BRCA1 localization. *ASTRO Annual Meeting, September 2008.* ASTRO Basic Science Travel Grant.

5. **Yang, ES,** Nowsheen, S, Thotala, D, Hallahan, DE, Xia, F. Inhibition of GSK3˜ enhances repair of double strand breaks in hippocampal neurons. *Vanderbilt Research Forum, April 2009.* Elliot V. Newman Best Oral Presentation Award.

6. **Yang, ES**, Wang, H, Nam, EA, Wang, Y, Billheimer, D, Chakravarthy, AB, Brown, M, Haffty, B, Xia, F. Can sporadic breast cancers with genetically wild-type BRCA1 behave phenotypically like BRCA1-associated breast tumors? *ASTRO Annual Meeting, November 2009.*

7. **Yang, ES,** Nowsheen, S, Xia, F. Targeting BRCA1 localization to convert tumor cell susceptibility to PARP inhibition. *Mini Symposium, Radiation Research Society Annual Meeting, September 2010.*

8. **Yang, ES** and Willey, CD. Combined EGFR/PI3K/mTOR inhibition with radiation for locally advanced head and neck cancer. *Center for Clinical and Translational Science (CCTS) Concepts Meeting, October 2010.*

9. **Yang, ES.** Induced synthetic lethality with cetuximab and the PARP inhibitor ABT-888 in head and neck cancer. *UAB Head and Neck Cancer Research "Think Tank," October 2010.*

10. **Yang, ES,** Nowsheen, S, Xia, F. Targeting BRCA1 localization to convert tumor cell susceptibility to PARP inhibition. *ASTRO Annual Meeting, November 2010.*

11. **Yang, ES.** PARP inhibition in HER2+ breast cancer. *UAB Breast Cancer Working Group, December 2010.*

12. **Yang, ES.** Cetuximab induces synthetic lethality with PARP inhibition in head and neck cancer cells. *UAB Comprehensive Cancer Center Seminar Series, December 2010.*

13. **Yang, ES.** Advances in prostate cancer. *American Cancer Society Us Too Prostate Cancer Support Group, February 2011.*

14. **Yang, ES.** Synthetic lethality with PARP inhibition in sporadic cancer. *Clinical and Translational Research Concepts, UAB Comprehensive Cancer Center, March 2011.*

15. **Yang, ES.** Synthetic lethality with PARP inhibition in sporadic head and neck cancer. *UAB Head and Neck Working Group, March 2011.*

16. **Yang, ES.** Potential determinants of sporadic tumor susceptibility to PARP inhibition. *Molecular Pharmacology Seminar Series, April 2011.*

17. **Yang, ES.** Advances in breast cancer therapies. *Top Oncology Treatment Advances, Russell Medical Center, May 2011.*

18. **Yang, ES.** Personalized medicine for head and neck cancer. *Southeast Cancer Foundation, September 2011.*

19. **Yang, ES.** Targeting the epidermal growth factor receptor (EGFR) family to render tumor cells susceptible to poly (ADP-ribose) polymerase (PARP) inhibition. *Invited mini-symposium speaker, 14th International Congress of Radiation Research, Warsaw, Poland, September 2011.*

20. **Yang, ES.** Synthetic lethal interactions between EGFR and PARP inhibition in head and neck cancer. *Invited speaker, UAB Comprehensive Cancer Center Research Retreat, October 2011.*

21. Klepczyk, L, Nowsheen, S, Xia, F, **Yang, ES**. BRCA1 Nuclear Export Sensitizes Prostate Cancer Cells to Poly (ADP-ribose) Polymerase-1 (PARP1) Inhibition via the CRM1/exportin Pathway. *ASTRO Annual Meeting, October 2011.*

22. **Yang, ES.** C.A.M.S. Seminar. *Invited speaker, UAB MSTP Program Lecture Series, January 2012.*

23. **Yang, ES.** Advances in cancer research. *Invited speaker, Southeast Cancer Foundation Regional Oncology Active Research (R.O.A.R.) Gala, January 2012.*

24. **Yang, ES.** "PARP-etuating" DNA damage in tumors. *Science Hour, Department of Radiation Oncology, UAB, February 2012.*

25. **Yang, ES.** Cancer susceptibility to PARP inhibition: It's not all about DNA repair. *Invited speaker, UAB Comprehensive Cancer Center Experimental Therapeutics Seminar Series, February 2012.*

26. **Yang, ES.** Susceptibility of HER2+ breast cancer to PARP inhibition. *Invited speaker, Vanderbilt University Research Retreat, June 2012.*

27. **Yang, ES**, Nowsheen, S, Cooper, T, Bonner, JA, LoBuglio, AF. Human HER2+ breast tumor susceptibility to PARP inhibitors independent of a homologous recombination repair defect. *ASTRO Annual Meeting, October 2012.*

28. Bonner, JA, Trummell, H, Nowsheen, S, **Yang, ES**. The role of STAT-3 in cetuximab-induced radiosensitization in head and neck cancer cells. *ASTRO Annual Meeting, October 2012.*

29. Whitley, AC, Jackson, J, Trummel, H, Bonner, JA, **Yang, ES**. Erlotinib induces synthetic lethality with the poly (ADP-Ribose) polymerase (PARP) inhibitor ABT-888 in esophageal cancer. *ASTRO Annual Meeting, October 2012.*

30. **Yang, ES**. Synthetic lethal interactions between EGFR and PARP inhibition in triple negative breast cancers. *Translational Breast Cancer Research Consortium, November 2012.*

31. **Yang, ES**. Role of PARP inhibition in HER2 positive breast cancers. *Translational Breast Cancer Research Consortium, November 2012.*

32. **Yang, ES**. *Invited guest speaker, American Physician Scientist Association, UAB Chapter, January 2013.*

33. Yang, ES. Targeting DNA damage and checkpoint pathways. *UAB Breast SPORE, February 2013.*